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(71) Applicant *(for all designated States except US)*: LEK PHARMACEUTICAL & CHEMICAL CO. DD [SI/SI]; Verovskova 57, 1526 Ljubljana (SI).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: KOFLER, Bojan [SI/SI]; Podlubnik 301, 4220 Skofja Loka (SI). KOVACIC, Mateja [SI/SI]; Pod Akacijami 9, 1000 Ljubljana (SI).

(74) Agent: BROWNE, Robin, Forsythe; Urquhart-Dykes & Lord, Tower House, Merrion Way, Leeds LS2 8PA (GB).

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(54) Title: PHARMACEUTICAL SUSPENSION FORMULATION COMPRISING AMOXYCILLIN, CLAVULANIC ACID AND CELLULOSE

(57) Abstract

A liquid aqueous pharmaceutical suspension formulation containing as active ingredient amoxycillin trihydrate and potassium clavulanate, including an effective quantity of cellulose as sole filler and optionally including further excipients.

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PHARMACEUTICAL SUSPENSION FORMULATION COMPRISING AMOXYCILLIN, CLAVULANIC ACID AND CELLULOSE

This invention relates to liquid aqueous suspension or dispersion formulations, particularly to stable oral pharmaceutical formulations comprising amoxycillin trihydrate and potassium clavulanate. These may be referred to as co-amoxiclav formulations. The invention also relates to the powder formulations for reconstitution as aqueous suspensions, and the granulate formulations for preparation of aqueous dispersions.

Amoxycillin is a well known broad-spectrum semisynthetic betalactam antibiotic effective against many gram-positive and gram-negative microorganisms. In combination with the β-lactamase inhibitor clavulanic acid, amoxycillin is also active against bacterial strains which are normally resistant to betalactam antibiotics. Gastrointestinal intolerance is often reported in patients treated with antibiotics, especially in children and sensitive individuals. Thus, there is the need for developing effective stable pharmaceutical formulations containing amoxycillin and clavulanic acid which have an acceptable taste and reduced gastrointestinal intolerance.

Sugars (such as glucose, fructose, lactose and maltose) and polyols (such as mannitol, sorbitol and xylitol) are often used as excipients in pharmaceutical formulations for preparation of powders for reconstitution as suspensions or granulates for preparation dispersions in water. Sugars and polyols endow the pharmaceutical product with a pleasant taste which is very important in pediatric use. When used in greater quantities as fillers in oral formulations, they have a laxative effect.

In order to minimise gastrointestinal intolerance of the amoxycillin/clavulanic acid suspensions, sugar or mannitol have been replaced with silicon dioxide. However these suspensions have a less pleasant taste.

Attempts have been made to reduce gastrointestinal side effects caused by the drugs containing amoxycillin plus clavulanic acid by using various additives. WO97/07408 discloses amoxycillin/clavulanic acid formulations to which pharmaceutically acceptable organic acid or salts thereof are added to reduce gastrointestinal intolerance. WO97/06798 discloses clavulanate formulations containing pharmaceutically acceptable salts of earth alkaline metals and inorganic acids to minimise gastrointestinal intolerance.

Addition of various metal salts, especially when greater amounts of silicon dioxide are present, potentiates an unpleasant taste making use of such formulations unacceptable.

According to a first aspect of the present invention a liquid aqueous pharmaceutical suspension or dispersion formulation contains as active ingredients amoxycillin trihydrate and potassium clavulanate, including an effective quantity of cellulose as sole filler and optionally including further excipients.

According to a second aspect of the present invention a dry powder or granule formulation is adapted upon addition of water to form a liquid aqueous pharmaceutical suspension in accordance with the first aspect of this invention.

Formulations in accordance with this invention provide an amoxycillin trihydrate/potassium clavulanate powder for reconstitution as a suspension and amoxycillin

trihydrate/potassium clavulanate granulates for preparing dispersions in water for oral administration which have reduced gastrointestinal intolerance and acceptable pleasant taste. The taste of the suspension is especially important in pediatric use. The aim of the invention is achieved by use of cellulose, either microcrystalline or powdered, as a sole filler. Generally other types of celluloses which have greater swelling ability, are used for preparation of suspensions in lower concentrations (0.2 to 5%) acting as viscosity-increasing agent (thickener). Microcrystalline cellulose is used primarily as a diluent in oral tablet and capsule formulations.

Microcrystalline cellulose with a particle size from 20 to 100 μm is preferred. Suitable grades include Avicel types pH 101, 102, 103, 104, 112, 113, 301 and 302. These differ in physical characteristics such as particle size, bulk density, los on drying, viscosity and chemical characteristics such as the degree of polymerisation

The percentages or amounts referred to in this specification are by weight unless indicated otherwise. Percentages or proportions are selected to total 100%.

In the formulations of this invention, predried cellulose (to reduce free water content which has an unfavourable impact on clavulanic acid stability) used as a filler acting simultaneously as a viscosity-increasing agent and a stabilising agent provides the good stability of the reconstituted suspension over the 7- to 10-day period of use. The amount of cellulose, as a principal filler in the formulation, may range from 5 to 70% w/w, preferably 20 to 70% w/w, more preferably 20 to 60% w/w of the dry

formulation. The percentage of the active substances is from 20 to 70%

Microcrystalline cellulose (Avicel, Emcocel, Vitacel) with an average particle size of 20 μm or preferably microcrystalline cellulose of average particle size of 50 μm may be used. Powdered cellulose (Vivacel, Elcema, Solka-Flok) having different particle size or as granulated powder may be used. In preferred embodiments the microcrystalline cellulose acts as a desiccant to protect the moisture sensitive clavulanate, leading to improved long term stability of the formulation.

Cellulose in the combination with sugars or polyols in the quantities devoid of a laxative effect may be used.

The formulations of this invention may also contain auxiliary ingredients which may be essentially conventional in the art. To improve the taste, flavours and sweetening agents, preferably saccharin, saccharin sodium or aspartame in the amounts allowable for oral formulations may be added. Flavours which may be used may comprise common flavours like strawberry, cherry, wild cherry, lemon, banana, raspberry, orange, caramel or mixtures thereof, which in combination with the antibiotic provide a pleasant flavour and taste.

Suitable excipients may include buffering agents such as different acids and their salts, eg citric acid, sodium citrate, succinic acid, swelling agents and viscosity-increasing agents such as suspension stabilisers and other additives.

The formulations of present invention are suitable for BID or TID administration in the prescribed dose. They are indicated in the treatment of children, adults and the elderly, and patients with difficulty in swallowing.

The present formulations relate to the combination of clavulanic acid and amoxycillin in a weight ratio of 1:1 to 1:20, preferably from 1:4 and 1:8. The formulations relate to the powder for suspension or granulation for dispersion in water for oral administration in the following doses:

Amoxycillin	Clavulanic acid
125 mg/5 ml	31.25 mg/5 ml
250 mg/5 ml	62.5 mg/5 ml
200 mg/5 ml	28.5 mg/5 ml
400 mg/5 ml	57 mg/5 ml
600 mg/5 ml	42.9 mg/5 ml
300 mg/5 ml	21.45 mg/5 ml

Other dosages may also be used.

The powder or the granulation should be stored in air-tight screwcap bottles or plastic containers or in sachets for preparation of suspension or dispersion, respectively, immediately prior to use.

The formulations of the present invention can be produced using the conventional manufacturing procedures such as homogenisation, sieving and milling. A portion of the ingredients may be pre-granulated, or granulated ingredients are used to improve powder flowability, which is especially important for sachet packaging.

Predried or anhydrous ingredients should be used in the formulation. Cellulose or a combination of cellulose and sodium carboxymethylcellulose should be dried in tray or vacuum dryers to LOD less than 1%. Additional drying of the

ingredients yields the powder and or granulate respectively, with a low moisture content, eg below 6%.

Clavulanic acid and salts thereof are extremely sensitive to the presence of moisture and free water and undergo rapid hydrolytic degradation. Therefor, the formulations of this invention should be manufactured in suitable air-conditioned production areas with relative humidity (RH) less than 30% and temperature below 25°C.

The invention is further described by means of example, but not in any imitative sense.

Example 1

Four formulations of this invention with different assays of amoxycillin trihydrate and potassium clavulanate were prepared. Their compositions and the role of individual auxiliary substances are listed in the table below:

Ingredient	A mg/5ml	B mg/5ml	C mg/5ml	D mg/5ml
Amoxycillin in the from of trihydrate) - active substance	400.00	200.00	600.00	300.00
Clavulanic acid (in the form of potassium salt) - active substance	57.00	28.50	42.90	21.45
Citric acid - buffering agent	2.69	2.69	2.69	2.69

Sodium citrate - buffering agent	8.33	8.33	8.33	8.33
Microcrystalline cellulose and sodium carboxymethylcellulose - viscosity-increasing agent	28.10	28.10	28.10	28.10
Gum xanthan - viscosity-increasing agent	10.00	10.00	10.00	10.00
Colloidal silicon dioxide Silicon dioxide - thickener	16.67 216.60	16.67 216.60	16.67 216.60	16.17 216.60
Flavours, eg strawberry caramel	 13.30 15.00	 13.30 15.00	 13.30 15.00	 13.30 15.00
Sweetening agent, eg saccharin sodium	6.70	6.70	6.70	6.70
Cellulose (microcrystalline or powdered) - filler	to 1250.00	to 1000.00	1250.00	1000.00

Example 2

The following formulations were prepared conventionally as dry powder mixtures.

Ingredient	E mg/5ml	F mg/5ml
Amoxycillin (in the form of trihydrate	250.00	125.00
Clavulanic acid (in the form of potassium salt)	62.50	31.25
Citric acid	3.00	3.00
Sodium citrate	9.00	9.00
Microcrystalline cellulose and sodium carboxymethylcellulose	13.75	13.75
Gum xanthan	11.50	11.50
Colloidal silicon dioxide	9.00	9.00
Silicon dioxide	50.00	33.50
Flavours, eg strawberry, caramel	33.50	33.50
Saccharin sodium	5.00	5.00
Cellulose (microcrystalline or powdered)	to 1000	to 1000

These formulations were manufactured using the standard methods known in the art for the production of powders and granulations for reconstitution in an aqueous suspension or for preparing a dispersion in water.

The quantities of inactive ingredients listed may vary from formulation to formulation to achieve the most favourable composition of properties including taste, physical and chemical stability.

Various amounts and types of flavours as well as their combination may be used to achieve optimal taste and odour.

The results of 3 months' accelerated stability testing at 40°C and 75% rel. humidity showed that the formulation

with cellulose as the main diluent proved to have good stability in powder form as well as a reconstituted suspension.

CLAIMS

1. A liquid aqueous pharmaceutical suspension or dispersion formulation containing as active ingredient amoxycillin trihydrate and potassium clavulanate, including an effective quantity of cellulose as sole filler and optionally including further excipients.

2. A dry powder formulation adapted upon addition of water to form a liquid aqueous suspension or dispersion as claimed in claim 1.

3. A formulation as claimed in claim 1 or 2, wherein the cellulose is selected from microcrystalline cellulose, powdered cellulose and mixtures thereof.

4. A formulation as claimed in any preceding claim, wherein the amount of cellulose is 5 to 60% by weight of the dry formulation.

5. A formulation as claimed in any preceding claim wherein the amount of active ingredients is 20 to 70% by weight of the dry formulation.

6. A formulation as claimed in any preceding claim including microcrystalline cellulose having a particle size of 20 to 100 μm, preferably 20 to 50 μm.

7. A formulation as claimed in any preceding claim, including microcrystalline cellulose having a particle size of 50 μm.

8. A formulation as claimed in any preceding claim wherein said further excipients include one or more sugars devoid of laxative effect.

9. Use of a formulation as claimed in any preceding claim for treatment of bacterial infections in paediatric and sensitive adult patients.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K47/38 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 34605 A (BAX RICHARD P ;SMITHKLINE BEECHAM PLC (GB); SMITHKLINE BEECHAM COR) 7 November 1996 (1996-11-07) page 6-8	1-5,8,9
Y		6,7
X	WO 97 06798 A (CROWLEY PATRICK JOHN ;SMITHKLINE BEECHAM PLC (GB)) 27 February 1997 (1997-02-27) cited in the application page 5, line 32 -page 6, line 5 page 11, line 1-16; claims 1-9	1-5,8,9
Y		6,7
P,X	WO 98 36732 A (POSANSKI ULRICH ;GLF GALENIK LABOR GMBH (DE)) 27 August 1998 (1998-08-27) page 11; example 2	1-9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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International Application No
P../GB 99/02295

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 35672 A (SANROMA BORDALLO JOSE LUIS ;SMITHKLINE BEECHAM S A (ES); MENTION J) 20 August 1998 (1998-08-20) claims 1-11 page 6, line 30-35 page 21; example 9	1-9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/02295

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